CDC National Children's Study Hypotheses Project

Systematic Literature Review

Contract Number HHS-100-97-0016

Prepared For:
National Center for Health Statistics,
Centers for Disease Control and Prevention

Prepared By:
The Lewin Group, Inc.

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I. OVERVIEW

The Lewin Group (Lewin) is conducting a systematic review to identify potential focal research areas and related hypotheses for inclusion in the National Children's Study, the proposed longitudinal cohort study of environmental influences on child health and development. The current report summarizes the methodology and results of Lewin's review of the scientific literature to identify research areas that suggest a need for further study. The report describes Lewin's methodology for reviewing relevant literature, summarizes the research areas of 49 articles selected for in-depth review, and concludes with a brief description of Lewin's next steps in developing hypotheses for the National Children's Study.

II. LITERATURE REVIEW METHODOLOGY

Adhering to the literature search strategy outlined in Lewin's previous memorandum (dated February 8, 2002), Lewin followed three basic steps to identify priority research areas and relevant articles to inform the development of potential hypotheses for the longitudinal study. Our strategy included:

Step 1: Identifying relevant current and proposed research areas

Step 2: Conducting a targeted search of bibliographic databases

Step 3: Categorizing search results for the in-depth literature review

This section details each step, including search and exclusion criteria, for reviewing the literature on environmental threats to children's health.

Step 1: Identify relevant current and proposed research areas

Lewin first examined the focal research areas and agenda of federal agencies, foundations with grant programs targeting issues related to women's and/or children's health, national professional associations focused on health-related issues for women and children, and several reports generated by the federal government. Given the broad range of topics covered by each of these organizations and reports, Lewin specifically searched for and examined research and agenda items related to environmental influences and child health and development. The following list indicates the agencies and organizations examined for this task.

- Environmental Protection Agency (EPA)
- National Center for Environmental Health, Centers for Disease Control and Prevention (NCEH/CDC)
- National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention (NCBDDD/CDC)
- Office on Women's Health, Centers for Disease Control and Prevention (OWH/CDC)
- National Institute of Environmental Health Sciences (NIEHS)
- National Institute of Child Health and Human Development (NICHD)

- National Cancer Institute (NCI)
- National Institute of Mental Health (NIMH)
- Maternal and Child Health Bureau, Health Resources and Services Administration (MCHB/HRSA)
- Agency for Toxic Substances and Disease Registry (ATSDR)
- Food and Drug Administration (FDA)
- American Academy of Pediatrics (AAP)
- American Public Health Association (APHA)
- Robert Wood Johnson Foundation (RWJ)
- Institute of Medicine (IOM)
- Healthy People 2000 & 2010
- Children's Defense Fund

In an effort to represent the multitude of organizations involved in child health and development research, Lewin also considered the Surgeon General's reports as well as the research priorities of other federal and non-federal entities, including the National Institute on Drug Addiction, the National Institute on Alcohol Abuse and Alcoholism, the Annie B. Casey Foundation and the David and Lucille Packard Foundation. Additionally, Lewin examined an existing inventory of longitudinal studies compiled in 2000 for a previous study for the National Center for Health Statistics. These organizations and studies, however, focused on health topics that have been well established in the scientific literature, such as the effects of smoking and alcohol on infant and child development, and issues relating to improving health policy and services for children. These sources did not indicate a particular emphasis on an area of research that would inform the development of new hypotheses on environmental effects on child health and development.

Lewin objectively considered the multitude of child health research topics and prioritized the literature based on several inclusion and exclusion criteria. Some of the inclusion criteria include:

- The magnitude of the population affected,
- Severity of the disease,
- The prevalence of the environmental exposure, and
- National Children's Study design considerations.

To exclude less relevant literature, Lewin considered the extent to which research had previously been conducted (i.e., hypotheses have been tested and supported and/or results have been extensively published) on a given topic area.

Lewin's initial search results revealed a common set of seven broad domains that were identified across organizations. These domains each encompass a wide range of environmental influences

and effects on child health and development, and were used for subsequent targeted literature searches:

- Asthma and respiratory illnesses
- Biobehavioral development
- Childhood cancers
- Endocrine disruptors
- Environmental toxicants
- Injury
- Neurodevelopment

Exhibit 1 indicates the research priorities for each of the relevant federal agencies, foundations, associations, and government reports reviewed.

Exhibit 1: Research Areas of Priority by Organization

Organizations	Priority and/or Current Research Areas						
	Asthma and Respiratory Illnesses	Biobehavioral Development	Childhood Cancers	Endocrine Disruptors	Environmental Toxicants	Injury	Neurodevelopment Disorders
NCEH/CDC	✓			✓	✓		✓
NCBDD/CDC					✓		✓
OWH/CDC				✓	✓		
NIEHS/NIH	✓		✓		✓		✓
NICHD/NIH		✓				✓	✓
NCI/NIH			✓		✓		
NIMH/NIH		✓				✓	✓
MCHB/HRSA	✓					✓	
EPA	✓		✓	✓	✓		✓
ATSDR	✓		✓	✓	✓		✓
FDA			✓	✓	✓		✓
AAP	✓	✓	✓		✓	✓	✓
APHA					✓		
RWJ						✓	
IOM	✓				✓		✓
Healthy People 2000/2010	✓					✓	✓
Children's Defense Fund	✓				✓	✓	

Step 2. Literature searches of bibliographic databases

After identifying priority research areas in children's health and environmental influences in Step 1, Lewin conducted a series of searches of seven databases to surface articles related to the eight identified, broad research domains, and additionally, to determine whether other priority areas emerged from the literature. Lewin examined and utilized the following bibliographic databases to identify scientific literature on children's health and environmental influences:

- MEDLINE: biomedical journals
- TOXNET: toxicology data network of the National Library of Medicine (NLM) (including TOXLINE, EMIC, DART/ETIC)
- EMBASE: biomedical and drug literature
- BIOSIS Previews: biological sciences literature
- Science Citation Index: scientific and technical journals
- Social Sciences Index: social science journals
- Enviroline: environmentally-related literature

The databases were searched concurrently to avoid duplicative results so that citations found in multiple databases were listed only once in the search results.

Selection and Exclusion Criteria

In order to identify pertinent abstracts for article retrieval, Lewin developed three levels of criteria, which are described below. Titles and descriptors from each citation were examined, and citations were excluded using the following Level 1 criteria:

- Study cohort could be identified as outside the scope of NCS (e.g., young adults or older teenagers);
- Study could be identified as occurring in a non-industrialized country;
- Publication type could be identified as a letter to the editor or a commentary (i.e., the publication did not focus on a study or specific research);
- Study could be identified as more technical or scientific in nature (e.g., descriptors were of chemical structures or mechanisms).

After applying Level 1 criteria, Lewin retrieved the abstracts of the remaining citations. Abstracts were reviewed and excluded using both Level 1 and Level 2 criteria, which include:

- No cause and effect relationship was identified or examined;
- Timing of exposure was not prenatal, postnatal or in early childhood;
- Study cohort was not pregnant women, or infants, or young children;
- Study was policy-oriented and did not offer direction for new research; and

- Study used animal models but did not discuss implications for humans.

Once articles were retrieved from the selected abstracts, Lewin read and reviewed the articles applying both Levels 1 and 2 criteria, in addition to a third level of criteria:

- Excluding articles that reported findings that already were well established;
- Excluding articles in which the environmental exposure was discussed without reference to a health or developmental outcome;
- Excluding studies on animals that did not transfer readily to humans; and
- Selecting articles that provided a representative sampling of the array of topics that surfaced in the literature. For example, we selected asthma studies focusing on different types of environmental exposure rather than include several studies focusing on the same exposure to reflect the various issues within "asthma" in need of further research. [1]

Lewin conducted three rounds of literature searches, each having a unique focus and applying a different level of specificity for identifying relevant research. Each search primarily scanned review and meta-analysis articles, which were more likely to yield multiple hypotheses and represent broader research interests rather than the more focused, original studies.

Round 1: Broad Literature Search

First Lewin conducted a broad and comprehensive search of the literature to substantiate the research areas identified in Step 1 of our review methodology, as well as to identify additional research areas in children's health and the environment which may have not been captured in Step 1. The following general parameters were applied to focus specifically on research areas of current and emerging interest for the child and environmental health research field:

- Review articles only
- Published from 1999 to the present
- English language only
- The search terms "environmental influence" OR "environmental effect" OR "environmental risk factor" OR "environmental exposure" were used in combination with each of the following:
    - (child health OR child development)
    - (infant health OR infant development)
    - (mother's health OR maternal health)
    - (fetal OR prenatal OR postnatal development)
    - (pregnancy AND infant)

[1] Lewin retained all relevant articles to assist in hypothesis generation and support; however, only the 36 articles selected for in-depth review are presented in this report.

Lewin utilized the truncation technique to capture all the variations of a search term so that the term "environment" would also retrieve "environments," "environmental" or "environmentally".

This broad search yielded 55 citations for review articles. Level 1 criteria were applied to titles and descriptors for these articles, and resulted in the exclusion of 33 articles from this pool.

Lewin then retrieved abstracts for the remaining 22 articles, reviewed the abstracts, and excluded studies based on both Level 1 and Level 2 criteria. A total of nine articles were yielded for in-depth review using Level 3 criteria. Seven of these articles were found to provide relevant information and have been included in the final list of search results.

Round 1 of the literature search directed Lewin's effort to target specific areas in children's health and environmental influences for further examination and confirm research areas identified from pertinent agencies and organizations in Step 1.

Round 2: Targeted Literature Search

Lewin then conducted a more targeted search of relevant databases in the areas of neurodevelopment, asthma, environmental toxicants, childhood cancers, endocrine disruptors, injury and behavior. The following search parameters guided Round 2's literature search:

- Published in 1996 to the present
- Published in English language only
- The search terms (environment influence OR effect OR risk factor OR exposure) AND (child OR infant OR prenatal) were used in combination with each of the following terms:
    - neurodevelopment
    - asthma
    - toxins
    - cancer
    - endocrine
    - behavior
    - social behavior

The search terms were used with a truncation technique and in various combinations, as described for the Round 1 literature search.

Round 2's targeted search yielded approximately 1,089 citations for articles published from 1996 to the present. Lewin applied Level 1 criteria to these citations, and obtained abstracts from 295 of these citations. Once abstracts were retrieved, Levels 1 and 2 criteria were applied and yielded 76 articles for retrieval and further review. Applying Level 3 criteria resulted in the selection of 36 articles.

Round 3: Literature Search Focused on Injuries

Though recent research has suggested that unintentional injury is the leading cause of childhood mortality, the initial searches yielded limited articles pertaining to the potential environmental causes or risk factors for injury. As such, Lewin conducted a third search using the following parameters:

- Search terms injury AND child OR infant OR prenatal
- Review articles only
- Published in 2000 to the present
- Published in English language only

Round 3's search yielded 575 citations. Lewin determined that this search included injury-related literature which was more relevant to the purpose of this project than what was previously yielded in Round 2.

To select articles for inclusion in our review, Lewin applied Level 1 criteria to the citations and retrieved 50 abstracts for further review. Levels 1 and 2 criteria were then applied to the abstracts. In addition to these criteria, Lewin also excluded abstracts based on the following criteria:

- Publication focused solely on sports-related injuries;
- Research focused on more biological injuries (i.e., disruption in molecular or biological pathways) which were similar in subject matter from previous searches. Instead, Lewin focused on injury research that presented as physical trauma, accidents, and/or results of maltreatment or abuse.

Application of these criteria resulted in the identification and retrieval of ten articles for in-depth review. Six studies were identified using Level 3 criteria. These six studies represent various issues (e.g., maltreatment, abuse, stress, socioeconomic factors, and built environment) related to childhood injury.

Step 3. Categorize search results for in-depth literature review

Steps 1 and 2 produced a set of 49 research articles and reports that focus on environmental threats to children's health and development. The majority (N=35) of these were review articles, which tend to span a subset of studies and yield multiple relevant hypotheses. We also included two meta-analytic articles, two reports from conferences, and 10 articles that described original research.

Lewin categorized the selected articles according to (a) research area, (b) type of environmental exposure, and (c) timing of the exposure, each of which is defined below.

(a) *Research Area* indicates the primary focus of the research reported in the article. The articles are categorized using the original seven research domains identified in Step 1, and an additional "other" category that captures additional research areas that emerged.

- Asthma and respiratory illnesses;
- Biobehavioral development, which focuses on cognitive, learning, emotional, social, and physical behaviors and susceptibility to behavioral disorders; includes conduct disorders, hyperactivity, attention deficit and hyperactivity disorder, anti-social or violent behaviors.
- Childhood cancers, including leukemia, brain and other tumors and increased risk for particular types of cancer (e.g., testicular cancer in young men).
- Endocrine disruptors, including DDT, diethylstilbestrol (DES), polychlorinated biphenyls (PCBs), and dioxins;
- Environmental toxicants, including pesticides, particulate matter, polycyclic aromatic hydrocarbons (PAHs), lead, and methylmercury;
- Injury, including unintentional injury, violence, abuse, maltreatment;
- Neurodevelopment, including neurodevelopmental disorders; and
- "Other" research areas, which capture additional important and emerging areas in child health and development (e.g., childhood obesity). Lewin included articles on obesity to reflect the research devoted to the subject of genetic and environmental influences on childhood obesity.

Lewin's classification system allowed for overlap between categories; research areas are not mutually exclusive. For example, Lewin classified a study that investigates the relationship between electromagnetic fields and childhood cancer in both the c*hildhood cancer* and e*nvironmental toxicants* research areas.

(b) *Type of Environmental Exposure* indicates the underlying nature of the exposure to the environmental threat:

- Physical: Describes exposures to the physical, ambient, surrounding environment (e.g., noise, ultrasound, pollution, radiomagnetic waves, radiation).
- Chemical: Describes exposures to chemical contact or intake (e.g., toxins, pesticides, metals, organic chemicals, and other relevant chemicals).
- Biological: Describes exposures to biological agents related to genetic or physiological pathways (e.g., infections, viruses, genetics, metabolic pathways, bacteria).
- Behavioral: Describes exposures that arise from behavioral activity by the child or the parent and interaction between parent and child (e.g., prenatal care, diet, smoking, exercise, abuse, neglect, parent-child interaction).

- Sociocultural: Describes exposures related to broader societal or cultural factors (e.g., socioeconomic status, ethnicity and cultural differences, daycare utilization, institutional/ policy factors).

(c) *Timing of Exposure* indicates whether exposure to the environmental threat occurred in utero, after birth, or during early to late childhood.

For each article, reviewed Lewin also identified the independent (typically the type of exposure) and dependent (typically the specific disease area, illness or disorder) variables and the cohort studied (infants, children, pregnant women).

Exhibit 2 categories the information recorded for each of the 49 articles Lewin selected for in-depth analysis.

RESEARCH AREAS:

1. Neurodevelopment
2. Childhood Cancers
3. Environmental Toxicants
4. Endocrine Disruptors
5. Injury
6. Asthma and Respiratory Ilnesses
7. Biobehavioral Development
8. Other

TYPE OF ENVIRONMENTAL EXPOSURE: Definitions and Examples

Physical: Includes exposures that stem from the physical, surrounding environment (e.g., Noise, ultrasound, air pollution, radiomagnetic waves, radiation, ozone, allergens, environmental tobacco smoke)
Chemical: Includes exposures that stem from chemical contact or intake
(e.g., Toxins, pesticides, metals, organic chemicals, and other relevant chemicals)
Biological: Includes exposures that stem from biological agents, related to genetic or physiological pathways
(e.g., infections, viruses, genetics, metabolic pathways, bacteria)
Behavioral: Includes exposures which arise as a consequence of behavioral activity by the child or the parent and interaction between parent and child
(e.g., Prenatal care, diet, smoking, exercise, abuse, neglect, parent-child interaction)
Sociocultural: Includes exposures which pertain to greater societal or cultural factors
(e.g., Socioeconomic status, ethnicity and cultural differences, daycare utilization, institutional/policy factors)

LITERATURE SOURCE

O=Original Research
R=Review
M=Meta-analysis
C=Conference abstract

	Citation by Research Area	RESEARCH AREAS								Exposure (independent variable/cause)	Disease area/focus (dependent variable/ effect)	TYPES OF ENVIRONMENTAL EXPOSURES					TIMING OF EXPOSURE			Cohort	Literature Source
		Neurodevelopment	Childhood Cancers	Environmental Toxicants	Endocrine Disruptors	Injury	Asthma and Respiratory Illnesses	Biobehavioral Development	Other			Physical	Chemical	Biological	Behavioral (M) = Mother (C) = Child	Sociocultural	Prenatal	Postnatal	Early to Late childhood		
	TOTAL	13	10	29	10	7	12	8	2								30	23	27		
1	Abramson MJ, Walters EH. The epidemic of asthma: too much allergen or not enough infection? Medical Journal of Australia 2000 Feb 7;172(3):119-21.						X			Allergens	Asthma	Dust mites, pollutants	Irritants	Infections				X		Infants, children	R
2	Ahlbom IC, Cardis E, Green A, Linet M, Savitz D, Swerdlow A. Review of the epidemiologic literature on EMF and Health. Environmental Health Perspectives 2001;109 Suppl 6:911-33.		X	X						Residential and occupational electromagnetic field exposure	Childhood cancer; adverse pregnancy outcomes (e.g., spontaneous abortion, low birth weight/premature delivery, etc.)	Electromagnetic fields					X	X		Pregnant women, infants	R
3	Akingbemi BT, Hardy MP. Oestrogenic and antiandrogenic chemicals in the environment: effects on male reproductive health. Annals of Medicine 2001;33(6):391-403.				X					Endocrine disruptors	Reproductive development		Phthalate esters, metabolites		Soy products (in diet) (M)			X		Mothers and infants	R
4	Alexander FE. Clusters and clustering of childhood cancer: a review. European Journal of Epidemiology 1999;15(9):847-52.		X							Infectious agents	Childhood cancer			Unspecified			X			Men and women of child-bearing age, pregnant women, infants, children	R

	Citation by Research Area	RESEARCH AREAS								Exposure (independent variable/cause)	Disease area/focus (dependent variable/ effect)	TYPES OF ENVIRONMENTAL EXPOSURES					TIMING OF EXPOSURE			Cohort	Literature Source
		Neurodevelopment	Childhood Cancers	Environmental Toxicants	Endocrine Disruptors	Injury	Asthma and Respiratory Illnesses	Biobehavioral Development	Other			Physical	Chemical	Biological	Behavioral (M) = Mother (C) = Child	Sociocultural	Prenatal	Postnatal	Early to Late childhood		
	TOTAL	13	8	28	9	7	11	8	2								28	20	27		
5	Boffetta P, Tredaniel J, Greco A. Risk of childhood cancer and adult lung cancer after childhood exposure to passive smoke: a meta-analysis. Environmental Health Perspectives 2000 Jan;108(1):73-82.		X	X						Environmental tobacco smoke (ETS)	Childhood Cancer	Passive smoking			Active smoking during pregnancy (M)		X	X	X	Pregnant women, infants, children	M
6	Bolande RP. Prenatal exposures and childhood cancer. Pediatric and Developmental Pathology 1999;2(3):208-14.		X	X	X					Preconceptional and parental exposure to electromagnetic fields, paint, hydrocarbon, cigarette smoke, etc.	Childhood tumors	Electromagnetic fields	DES, hydrocarbons, nitro and aromatic amino compounds; insecticides		Smoking, alcohol, barbiturates, amphetamines, coffee, analgesics		X	X		Pregnant women, infants, children	R
7	Bove F, Shim Y, Zeitz P. Drinking water contaminants and adverse pregnancy outcomes: a review. Environmental Health Perspectives 2002;110:61-74.			X						Drinking water contaminants (e.g., chlorination disinfection by-products)	Adverse birth outcomes (e.g., NTDs, low birth weight, spontaneous abortions)		Trihalo-methanes, trichloroethylene				X			Pregnant women, infants	R
8	Bowman P, Oblender M, Oeffinger KC, Ward J. Childhood cancer and environmental toxins: the debate continues. Family & Community Health 2002 Jan;24(4):27-38.		X	X						EMFs, radon, pesticides, solvents, parental occupational exposure, diet, ETS, alcohol, and infection	Childhood leukemia	Electromagnetic fields, radon, environmental tobacco smoke	Pesticides	Infection	Parental occupational exposure, diet (M), alcohol (M)		X	X	X	Pregnant women, infants, children	R
9	Breier BH, Vickers MH, Ikenasio BA, Chan KY, Wong WPS. Fetal programming of appetite and obesity. Molecular and Cellular Endocrinology 2001 Dec 20; 185(1-2);73-79.								X	Diet	Appetite and obesity and metabolic disorders				Diet (M)		X			Animal models	R
10	Bremne JD, Vermetten E. Stress and development: behavioral and biological consequences. Developmental Psychopathology 2001Summer; 13(3):473-489.	X				X		X		Child abuse	Neurobiological development and its effects on behavior and biological processes.				Maternal separation, childhood abuse			X	X	Animal studies, patients with history of abuse	R

	Citation by Research Area	RESEARCH AREAS								Exposure (independent variable/cause)	Disease area/focus (dependent variable/ effect)	TYPES OF ENVIRONMENTAL EXPOSURES					TIMING OF EXPOSURE			Cohort	Literature Source
		Neurodevelopment	Childhood Cancers	Environmental Toxicants	Endocrine Disruptors	Injury	Asthma and Respiratory Illnesses	Biobehavioral Development	Other			Physical	Chemical	Biological	Behavioral (M) = Mother (C) = Child	Sociocultural	Prenatal	Postnatal	Early to Late childhood		
	TOTAL	12	5	24	8	6	11	7	1								23	16	24		
11	Brenner RA, Overpeck MD, Trumble AC, DerSimonian R, Berendes H. Deaths attributable to injuries in Infants, United States, 1983-1991. Pediatrics 1999 May;103 (5): 968-974.					X				Physical and sociodemographic factors	Injury related deaths	Inhalation of foods and objects			Homicide, motor vehicle crashes,	Education, race, ethnicity	X	X		Pregnant women, infants, mothers	C
12	Carpenter DO. Effects of metals on the nervous system of humans and animals. International Journal of Occupational Medicine and Environmental Health 2001;14(3):209-18.	X		X				X		Lead and mercury	Exposure to lead resulting in lowered IQ, and behavior and attention problems in childhood and reduced cognitive functioning and anti-social		Lead, methyl-mercury						X	Children	R
13	Caspi A, Taylor A, Moffitt TE. Neighborhood deprivation affects children's mental health: environmental risks identified in a genetic design. Psychological Science 2000 Jul;11(4):338-42.							X		Social and genetic characteristics and genetic predisposition	Mental health			Genetic pre-disposition		Neighborhood conditions: housing tenure/dwelling type, unemployment status, car availability, educational qualifications, socio-economic differences			X	Children (twins)	O
14	Cohen HEA, Sheldon LS, Burke JM, McCurdy TR, Berry MR, Rigas ML, et al. Children's exposure assessment: a review of factors influencing children's exposure, and the data available to characterize and assess that exposure.			X						Chemicals in air and food, play areas; children's diet; socioeconomic factors and race/ethnicity	Child health and development	Environmental tobacco smoke	Pesticides, lead, methyl-mercury; house dust, soil		Diet (M)	Socio-economic factors and race/ethnicity	X	X	X	Pregnant women, mothers, infants children	R
15	Cummins SK, Jackson RJ. The built environment and children's health. Pediatric Clinics of North America 2001;48(5):1241-52.					X				Risk factors in children's built environment	Children's injury and disability	Design of housing, urban land use							X	Children	R

	Citation by Research Area	RESEARCH AREAS								Exposure (independent variable/cause)	Disease area/focus (dependent variable/ effect)	TYPES OF ENVIRONMENTAL EXPOSURES					TIMING OF EXPOSURE			Cohort	Literature Source
		Neurodevelopment	Childhood Cancers	Environmental Toxicants	Endocrine Disruptors	Injury	Asthma and Respiratory Illnesses	Biobehavioral Development	Other			Physical	Chemical	Biological	Behavioral (M) = Mother (C) = Child	Sociocultural	Prenatal	Postnatal	Early to Late childhood		
	TOTAL	11	5	22	8	4	11	5	1								21	14	20		
16	Denson KWE. Passive smoking in infants, children and adolescents. The effects of diet and socioeconomic factors. International Archives of Occupational and Environmental Health 2001;74(8):525-532.			X			X			Environmental tobacco smoke, behavioral, and socioeconomic factors	Asthma and Respiratory Illness	Environmental tobacco smoke			Diet (intake of vegetables/ fruit) (M), lifestyle of smoker (M)	Socio-economic factors	X	X	X	Infants, children, adolescents	R
17	Douwes J, Pearce N, Heederik D. Does environmental endotoxin exposure prevent asthma? Thorax 2002 Jan;57(1):86-90.			X			X			Environmental endotoxin exposure	Asthma			Bacteria endotoxins (farms)					X	Children, adolescents	R
18	Eggleston PA, Buckley TJ, Breysse PN, Wills-Karp M, Kleeberger SR, Jaakkola JJ. The environment and asthma in U.S. inner cities. Environmental Health Perspectives 1999 Jun;107 Suppl 3:439-50.			X			X			Air pollution, ozone, and psychosocial factors	Asthma	Ozone	Pollutants, particulate matter	Genetics	Depression, anxiety, changing pattern of behavior	Stress from living in the inner city, poor access to health care, poverty, education	X	X	X	Pregnant women, mothers, fetus, infants, children	R
19	Eskenazi B, Castorina R. Association of prenatal maternal or postnatal child environmental tobacco smoke exposure and neurodevelopmental and behavioral problems in children. Environmental Health Perspectives 1999 Dec;107(12):991-1000.	X		X				X		Environmental tobacco smoke (passive and maternal active smoking)	Neurodevelopment and behavioral health	Environmental tobacco smoke			Smoking (M)		X	X		Pregnant women, infants, children	R
20	Feeley M, Brouwer A. Health risks to infants from exposure to PCBs, PCDDs and PCDFs. Food Additives and Contaminants 2000 Apr;17(4):325-33.	X			X					In utero exposure to and breast-milk contaminated with PCBs, PCDDs, PCDFs	Developmental effects in children (e.g., low birth weight, psychomotor and cognitive function delays)		PCBs, dioxins				X	X		Pregnant women, mothers, infants	R

	Citation by Research Area	RESEARCH AREAS								Exposure (independent variable/cause)	Disease area/focus (dependent variable/ effect)	TYPES OF ENVIRONMENTAL EXPOSURES					TIMING OF EXPOSURE			Cohort	Literature Source
		Neurodevelopment	Childhood Cancers	Environmental Toxicants	Endocrine Disruptors	Injury	Asthma and Respiratory Illnesses	Biobehavioral Development	Other			Physical	Chemical	Biological	Behavioral (M) = Mother (C) = Child	Sociocultural	Prenatal	Postnatal	Early to Late childhood		
	TOTAL	9	5	18	7	4	8	4	1								17	10	17		
21	Gitterman BA, Bearer CF. A developmental approach to pediatric environmental health. Pediatric Clinics of North America 2001 Oct;48(5):1071-83.			X	X					Environmental toxic substances	In utero development; newborn infant growth; health during preschool- and school-ages	Environmental tobacco smoke	PCB, lead poisoning, iodine, disinfectants		Smoking (M)		X	X	X	Pregnant women, infants, children	R
22	Glaser D. Child abuse and neglect and the brain--a review. Journal of Child Psychology and Psychiatry 2000;41(1): 97-116.					X				Child abuse and neglect	Deleterious effects on child's brain including brain volume and structural changes				Maltreatment of children (M)				X	Children	R
23	Gold DR. Environmental tobacco smoke, indoor allergens, and childhood asthma. Environmental Health Perspectives 2000 Aug;108 Suppl 4:643-51.						X			Environmental tobacco smoke and indoor allergens	Asthma	Environmental tobacco smoke, dust mite, cockroach, and cat allergens		Genetic pre-disposition					X	Children	R
24	Goldsmith CA, Kobzik L. Particulate air pollution and asthma: a review of epidemiological and biological studies. Reviews on Environmental Health 1999			X			X			Air pollution (reducing type from pollution combustion and photochemical pollution from reactions involving UV	Asthma	Fossil Fuel, smelting, petrochemical refining, photooxidation, ozone, UV light							X	Children	R
25	Gressens P, Mesples B, Sahir N, Marret S, Sola A. Environmental factors and disturbances of brain development. Seminars in Neonatology 2001;6(2):185-94.	X		X				X		Recreational drugs, illegal substances, smoking, sensory stimulations	Fetal Alcohol Snydrome, children's IQ level, hyperactivity, fine motor skill impairment, microcephaly, cerebral malformation, intrauterine growth retardation and conduct disorder, learning disability and attention deficits, holoprosencephaly, ocular devel	Monocular visual deprivation, mild to moderate noise, pre-term pain	Ethanol; opiates, cocaine, nicotine, lead and methylmercury	Maternal diabetes	Smoking (M)		X	X		Pregnant women, infants, children	R

	Citation by Research Area	RESEARCH AREAS								Exposure (independent variable/cause)	Disease area/focus (dependent variable/ effect)	TYPES OF ENVIRONMENTAL EXPOSURES					TIMING OF EXPOSURE			Cohort	Literature Source
		Neurodevelopment	Childhood Cancers	Environmental Toxicants	Endocrine Disruptors	Injury	Asthma and Respiratory Illnesses	Biobehavioral Development	Other			Physical	Chemical	Biological	Behavioral (M) = Mother (C) = Child	Sociocultural	Prenatal	Postnatal	Early to Late childhood		
	TOTAL	8	5	15	6	3	6	3	1								15	8	13		
26	Grossman DC. The history of injury control and the epidemiology of child and adolescent injuries. The Future of Children 2000;10(1):23-52.					X				Poverty levels and illegal substance use	Children's unintentional injury (e.g., motor vehicle accidents, drowning, poisonings)				Alcohol drinking (C)	Low-income family status			X	Children, adolescents, parents	R
27	Kilpelainen M, Terho EO, Helenius H, Koskenvuo M. Farm environment in childhood prevents the development of allergies. Clinical and Experimental Allergy 2000 Feb;30(2):201-8						X			Bacteria found in farm and rural settings (protective exposure)	Asthma, wheezing, atopic disorders			Mycobacteria, actinomycetes (protective)					X	Young Adults (18-24yrs old)	O
28	Laflamme L. Pupil injury risks as a function of physical and psychosocial environmental problems experienced at school. Journal of the International Society for Child and Adolescent Injury Prevention 2001 Jun;7(2):146-9.					X				Physical and psychosocial factors	Injury	Ventilation noise, ergonomic conditions, lighting			Sports, recess, physical violence injuries (C)				X	Children	O
29	Landrigan PJ. Children's environmental health. Lessons from the past and prospects for the future. Pediatric Clinics of North America 2001;48(5):1319-30.		X	X	X		X			Air pollution; endocrine disruptors; chemicals	Asthma, developmental disabilities, testicular cancer in young men, pediatric cancers	Allergens	Methylmercury, DES				X	X	X	Pregnant women, infants, children	R
30	Lanphear BP, Kahn RS, Berger O, Auinger P, Bortnick SM, Nahhas RW. Contribution of residential exposures to asthma in US children and adolescents. Pediatrics 2001 Jun;107(6): E98.			X			X			Environmental tobacco smoke, indoor allergens, outdoor pollution	Asthma	Pets, dust mite, cockroach, outdoor pollution, environmental tobacco smoke				Access to healthcare and urban status			X	Children, adolescents	O

	Citation by Research Area	RESEARCH AREAS								Exposure (independent variable/cause)	Disease area/focus (dependent variable/ effect)	TYPES OF ENVIRONMENTAL EXPOSURES					TIMING OF EXPOSURE			Cohort	Literature Source
		Neurodevelopment	Childhood Cancers	Environmental Toxicants	Endocrine Disruptors	Injury	Asthma and Respiratory Illnesses	Biobehavioral Development	Other			Physical	Chemical	Biological	Behavioral (M) = Mother (C) = Child	Sociocultural	Prenatal	Postnatal	Early to Late childhood		
	TOTAL	8	4	13	5	1	3	3	1								14	7	8		
31	London EA, Etzel RA. The environment as an etiologic factor in autism: a new direction for research. Environmental Health Perspectives 2000 Jun;108 Suppl 3:401-4.	X		X						Retinoic acid as an environmental disruptor in neural tube formation in the fetus through its possible role as a genetic modifier	Autism		Gene interaction with environmental retinoids				X			Pregnant women, infants, children	R
32	McConnell R, Berhane K, Gilliland F, London SJ, Islam T, Gauderman WJ, et al. Asthma in exercising children exposed to ozone: a cohort study. Lancet 2002 Feb 2;359(9304):386-91.			X			X			Ozone and other air pollutants and exercise or time spent outdoors	Asthma	Ozone	Air pollutants		Exercise (sports), time spent outside (C)				X	Children	O
33	Nevin R. How lead exposure relates to temporal changes in IQ, violent crime, and unwed pregnancy. Environmental Research 2000 May;83(1):1-22.	X		X				X		Lead exposure	Loss in IQ, violent crime, unwed pregnancy		Lead (gasoline lead exposure, lead paint)	Loss in IQ from lead exposure (leads to undesirable social behavior)					X	Children	O
34	Peden DB. Development of atopy and asthma: candidate environmental influences and important periods of exposure. Environmental Health Perspectives 2000 Jun;108 Suppl 3:475-82.			X			X			Air pollution and maternal behavior	Atopy and Asthma	Urban/rural setting, ozone, dust mites, pollen, orally encountered antigens		Genetic pre-disposition, infections	Parental influences, diet, exercise, maternal tobacco smoke		X	X	X	Fetus, infant, children	R
35	Pereira LAA, Loomis D, Conceicao GMS, Braga ALF, Arcas RM, Kishi HS, et al. Association between air pollution and intrauterine mortality in Sao Paulo, Brazil. Environmental Health Perspectives 1998 Jun;106(6):325-329.			X						Air pollution (NO_2, SO_2, CO, O_3, and particulate matter)	Intrauterine death		NO_2, SO_2, CO, O_3, Particulate matter				X			Pregnant women	O

	Citation by Research Area	RESEARCH AREAS								Exposure (independent variable/cause)	Disease area/focus (dependent variable/ effect)	TYPES OF ENVIRONMENTAL EXPOSURES					TIMING OF EXPOSURE			Cohort	Literature Source
		Neurodevelopment	Childhood Cancers	Environmental Toxicants	Endocrine Disruptors	Injury	Asthma and Respiratory Illnesses	Biobehavioral Development	Other			Physical	Chemical	Biological	Behavioral (M) = Mother (C) = Child	Sociocultural	Prenatal	Postnatal	Early to Late childhood		
	TOTAL	6	4	8	5	1	1	2	1								11	6	5		
36	Perera FP, Illman SM, Kinney PL, Whyatt RM, Kelvin EA, Shepard P, et al. The challenge of preventing environmentally related disease in young children: community-based research in New York City. Environmental Health Perspectives 2002;110(2):197-204.	X	X	X			X	X		Environmental toxicants, environmental tobacco smoke (ETS), gene-environment interaction, individual- and community-level psychosocial stressors	Allergic sensitization, asthma and other respiratory diseases, impairment of neurocognitive and behavioral development, and potential cancer risk.	Environmental tobacco smoke, indoor allergens (dust mite, mouse, cockroach)	Particulate matter, polycyclic aromatic hydrocarbons (PAHs), diesel exhaust particulate (DEP), nitrogen oxide, and lead and other metals such as mercury	Genetic pre-disposition	Nutrition (M)	Sociocultural stressors including living in violent, crime-ridden, physically-decayed neighborhoods	X	X		Pregnant women, infants	R
37	Reigart JR, Roberts JR. Pesticides in children. Pediatric clinics of North America 2001 Oct; 48(5):1185-98.		X	X	X					Pesticides, including endocrine disruptors	Childhood cancers (leukemia, brain tumors), altered sexual development and fertility		Pesticides						X	Children	R
38	Ross JA, Swensen AR. Prenatal epidemiology of pediatric tumors. Current Oncology Reports 2000 May;2(3):234-41.		X	X						Infectious agents, Radiation	Acute lymphoblastic leukemia	Radiation		Hepatitis, Mycoplasma pneumonia			X	X	X	Pregnant mothers, infants, children	R
39	Rubin CH, Niskar AS. Endocrine disruptors: an emerging environmental health problem. Journal of the Medical Association of Georgia 1999 Dec;88(4):27-30.	X			X					Endocrine disruptors	Birth defects, developmental disabilities		DDT, PCBs, dioxins				X			Pregnant women, infants	R
40	Schuz J, Grigat JP, Brinkmann K, Michaelis J. Residential magnetic fields as a risk factor for childhood acute leukemia: results from a German population-based case-control study. International Journal of Cancer 2001;91(5):728-35.		X	X						Power-frequency electromagnetic fields	Childhood leukemia	Electromagnetic fields							X	Children	O

	Citation by Research Area	RESEARCH AREAS								Exposure (independent variable/cause)	Disease area/focus (dependent variable/ effect)	TYPES OF ENVIRONMENTAL EXPOSURES					TIMING OF EXPOSURE			Cohort	Literature Source
		Neurodevelopment	Childhood Cancers	Environmental Toxicants	Endocrine Disruptors	Injury	Asthma and Respiratory Illnesses	Biobehavioral Development	Other			Physical	Chemical	Biological	Behavioral (M) = Mother (C) = Child	Sociocultural	Prenatal	Postnatal	Early to Late childhood		
	TOTAL	4	0	4	3	1	0	1	1								8	4	2		
41	Solomon GM, Schettler T. Environment and health: 6. Endocrine disruption and potential human health implications. Canadian Medical Association Journal	X			X					Endocrine disruptors	Birth defects, abnormal infant reproductive system development, neurobehavioral function		PCBs, dioxins, atrazine		Diet (M)		X	X		Pregnant women, mothers, infants children	R
42	Sovikova E. Environmental risk factors in mental development of children. Toxicology Letters 2000;116:72.	X		X						Lead, smoking, socioeconomic factors	Deficits in cognitive function in children		Lead		Smoking (M)	Income level, number or children, nutritional problems, education level			X	Children	C
43	Tickner JA, Schettler T, Guidotti T, McCally M, Rossi M. Health risks posed by use of Di-2-ethylhexyl phthalate (DEHP) in PVC medical devices: a critical review. American Journal of Industrial Medicine 2001;39(1):100-11.			X						Toxicity leach from medical devices	Developmental complications in multiple organ systems including liver, reproductive tract, kidneys, lungs and heart		Phthalate esters				X	X		Pregnant women, infants	M
44	Wadhwa PD, Sandman CA, Garite TJ. The neurobiology of stress in human pregnancy: implications for prematurity and development of the fetal central nervous system. Progress in Brain Research 2001; 133:131-142.	X				X				Maternal psychosocial stress and biological factors	Fetal developmental process			Maternal - placenta hormones	Maternal prenatal stress		X	X		Pregnant women, fetus, infants	R
45	Wasserman GA, Liu X, Pine DS, Graziano JH. Contribution of maternal smoking during pregnancy and lead exposure to early child behavior problems. Neurotoxicology and Teratology 2001;23(1):13-21.							X		Maternal smoking during pregnancy	Behavior problems in childhood (e.g., conduct disorder, ADHD)				Smoking during pregnancy (M)		X			Pregnant women, infants, children	O

	Citation by Research Area	RESEARCH AREAS								Exposure (independent variable/cause)	Disease area/focus (dependent variable/ effect)	TYPES OF ENVIRONMENTAL EXPOSURES					TIMING OF EXPOSURE			Cohort	Literature Source
		Neurodevelopment	Childhood Cancers	Environmental Toxicants	Endocrine Disruptors	Injury	Asthma and Respiratory Illnesses	Biobehavioral Development	Other			Physical	Chemical	Biological	Behavioral (M) = Mother (C) = Child	Sociocultural	Prenatal	Postnatal	Early to Late childhood		
	TOTAL	1	0	2	2	0	0	0	1								4	1	1		
46	Weber RFA, Pierik FH, Dohle GR, Burdorf A. Environmental influences on male reproduction. BJU International 2002;89(2):143-148.				X					Endocrine disruptors	Abnormal development of male reproductive tract		DES				X			Pregnant women, infants, children	R
47	Weiss B. Vulnerability of children and the developing brain to neurotoxic hazards. Environmental Health Perspectives 2000;108:375-81.	X		X	X					Chemical contaminants in the environment and socioeconomic factors	Neurobehavioral development		Lead, PCBs		Smoking (M)	Maternal and paternal intelligence, income level, maternal and paternal education, race, marital status, maternal age	X	X	X	Parents, pregnant women, infants, children	R
48	Whitaker RC, Dietz WH. Role of the prenatal environment in the development of obesity. Journal of Pediatrics 1998 May;132 (5):768-776.								X	Maternal obesity, weight gain during pregnancy, maternal diabetes during pregnancy	Altered fetal development leading to obesity in children			Maternal diabetes during pregnancy (M)	Maternal weight gain		X			Pregnant women, children	R
49	Zender R, Bachand AM, Reif JS. Exposure to tap water during pregnancy. Journal of Exposure Analysis and Environmental Epidemiology 2001;11(3):224-30.			X						Disinfection byproducts in drinking water	Adverse birth outcome		Disinfection byproducts (DBPs)				X			Pregnant women, infants	O

III. LITERATURE REVIEW FINDINGS

The literature review identified several areas of emphasis in the literature investigating environmental influences on children's health and development, including a focus on several disease areas, specifically asthma and childhood cancers, and neurological and biobehavioral developmental processes. The research implicates these areas as needing further study. Injury, the leading cause of childhood mortality, is also a critical area for continued exploration to identify causes and inform prevention and treatment strategies. Lewin also identified childhood obesity as a focal research area in need of continued exploration.

The diseases, illnesses, disorders and/or conditions served as dependent variables in the studies Lewin reviewed. The selected articles explored relationships between:

- ***Asthma*** and child (prenatal, postnatal and early childhood) or maternal exposure to indoor allergens, endotoxins, endocrine disruptors, infection, ozone, air pollution, ozone, and environmental tobacco smoke (passive smoking); maternal smoking and diet; child behavior (e.g., exercise/time spent outdoors); and genetic predisposition.
- ***Childhood cancer*** and child (prenatal, postnatal and early childhood) and parental exposure to electromagnetic fields, radiation, radon, hydrocarbons, nitro and amino compounds, infectious agents, paint, environmental tobacco smoke, air pollution, DES, insecticides and pesticides; and maternal smoking and diet.
- ***Childhood obesity*** and maternal obesity, maternal diabetes during pregnancy, maternal weight gain during pregnancy, and maternal diet.
- ***Neurodevelopment*** and child (prenatal, postnatal and early childhood) and maternal (during pregnancy) exposure to lead, methylmercury, PCBs, dioxins, retinoids, environmental tobacco smoke, and mild-to-moderate noise; child abuse; and maternal psychosocial stress, smoking and use of recreational and illicit drugs.
- ***Biobehavioral development*** and child (prenatal, postnatal and early childhood) and maternal (during pregnancy) exposure to lead, mercury, environmental tobacco smoke, particulate matter, and mild-to-moderate noise; and maternal smoking during pregnancy; genetic predisposition; socioeconomic and neighborhood factors (e.g., housing type, unemployment status, car availability); sociocultural stressors (e.g., living in violent, crime-ridden, or physically decayed neighborhoods); and child abuse.

Injury also emerged as an area in which insufficient understanding of the clear risk factors and causes highlights the need for further research. Childhood injury served as both a dependent and independent variable in the studies Lewin selected.

- Research identified a need for additional exploration into the mechanisms by which child abuse, stress and maltreatment have behavioral and biological consequences on children's developmental processes.
- Environmental factors including familial structure, characteristics of houses and urban settings, and socioeconomic status may place children at greater risk for unintentional injuries, including motor vehicle accidents, drowning, falls, and poisoning.

The literature indicates that *environmental toxicants*, including the subset of *endocrine disruptors,* have received a great deal of research attention as adversely affecting childhood health and development. The literature calls for further research to provide additional support for relationships between environmental toxicants (consistently the independent variables in research studies) and childhood asthma and respiratory illnesses; childhood cancers; birth defects; autism, neurodevelopmental disorders, cerebral malformation, cognitive functioning impairments; biobehavioral disorders, including conduct disorders, anti-social behavior, violent criminal activity, hyperactivity, attention deficit disorders; adverse pregnancy/birth outcomes, and child health and development.

The selected research investigated the following environmental toxicants:

- Air pollutants, including diesel exhaust particulate (DEP), polycyclic aromatic hydrocarbons (PAHs), carbon monoxide, nitrogen dioxide, sulfur dioxide, and ozone
- Alcohol (ethanol)
- Drugs (opiates, cocaine, nicotine)
- Endocrine disruptors (Atrazine, DES, DDT, PCBs, dioxins)
- Disinfectants/disinfectant byproducts (DBPs)
- Electromagnetic fields, radiation, ultraviolet light
- Environmental tobacco smoke
- Iodine
- Metals (e.g., lead and methylmercury)
- Noise (mild to moderate levels)
- Pesticides
- Retinoic acid (retinoids)

IV. NEXT STEPS

Based on the research identified and discussions with NCHS and identified experts in the field, Lewin will develop a series of hypotheses for consideration for the National Children's Study. Specifically, Lewin will identify hypotheses suggested by the reviewed articles, and will supplement this research with additional targeted small-scale searches, as necessary, to support justification for the significance or need to test specific hypotheses. Broad hypotheses will focus on the research domains (e.g., asthma, childhood cancer) identified through our literature review process; more detailed or narrower hypotheses will be developed within each research domain.

APPENDIX A

Abramson MJ, Walters EH. **The epidemic of asthma: too much allergen or not enough infection?** Medical Journal of Australia 2000 Feb 7;172(3):119-21.

Asthma has generally been thought to result from exposure to allergens in infancy leading to atopy, and eventually to airway hyperresponsiveness. There is now evidence that implicates absence of childhood infections as a factor in development of asthma. Childhood infections seem to be important in normal maturation of the immune system, with asthma a manifestation of a persistent "immature" immune system.

Ahlbom IC, Cardis E, Green A, Linet M, Savitz D, Swerdlow A. **Review of the epidemiologic literature on EMF and Health**. Environmental Health Perspectives 2001;109 Suppl 6:911-33.

Exposures to extremely low-frequency electric and magnetic fields (EMF) emanating from the generation, transmission, and use of electricity are a ubiquitous part of modern life. Concern about potential adverse health effects was initially brought to prominence by an epidemiologic report two decades ago from Denver on childhood cancer. We reviewed the now voluminous epidemiologic literature on EMF and risks of chronic disease and conclude the following: a) The quality of epidemiologic studies on this topic has improved over time and several of the recent studies on childhood leukemia and on cancer associated with occupational exposure are close to the limit of what can realistically be achieved in terms of size of study and methodological rigor. b) Exposure assessment is a particular difficulty of EMF epidemiology, in several respects: i) The exposure is imperceptible, ubiquitous, has multiple sources, and can vary greatly over time and short distances. ii) The exposure period of relevance is before the date at which measurements can realistically be obtained and of unknown duration and induction period. iii) The appropriate exposure metric is not known and there are no biological data from which to impute it. c) In the absence of experimental evidence and given the methodological uncertainties in the epidemiologic literature, there is no chronic disease for which an etiological relation to EMF can be regarded as established. d) There has been a large body of high quality data for childhood cancer, and also for adult leukemia and brain tumor in relation to occupational exposure. Among all the outcomes evaluated in epidemiologic studies of EMF, childhood leukemia in relation to postnatal exposures above 0.4 microT is the one for which there is most evidence of an association. The relative risk has been estimated at 2.0 (95% confidence limit: 1.27-3.13) in a large pooled analysis. This is unlikely to be due to chance but, may be, in part, due to bias. This is difficult to interpret in the absence of a known mechanism or reproducible experimental support. In the large pooled analysis only 0.8% of all children were exposed above 0.4 microT. Further studies need to be designed to test specific hypotheses such as aspects of selection bias or exposure. On the basis of epidemiologic findings, evidence shows an association of amyotrophic lateral sclerosis with occupational EMF exposure although confounding is a potential explanation. Breast cancer, cardiovascular disease, and suicide and depression remain unresolved.

Akingbemi BT, Hardy MP. **Oestrogenic and antiandrogenic chemicals in the environment: effects on male reproductive health**. Annals of Medicine 2001;33(6):391-403.

Exposures of human populations to pesticides and industrial pollutants, and to synthetic chemicals present in foods, beverages, and plastics, have raised concern that these substances can interfere with endogenous sex hormone function. Interference with sex hormone action can, in turn, result in a variety of developmental and reproductive anomalies. Compounds in this class

are thus referred to as endocrine disruptors (EDs). EDs that affect reproductive processes in vertebrates act primarily by altering oestrogenic and antiandrogenic activities. The recent cloning of a second oestrogen receptor (ER) subtype (ERbeta) and its widespread tissue distribution pattern indicates that the first ER to be cloned, ERalpha, may not be the only, or even the primary, mediator of oestrogen action. It is anticipated that this discovery will lead to development of antagonist compounds specific to either ER subtype, and help to determine the function of each receptor subtype in reproductive and other tissues. Growing evidence suggests that EDs interfere with reproductive function at low exposure levels and cause distinct effects at different concentrations within the same organ. Developing organisms have increased susceptibility to the actions of EDs because differentiating tissues are more vulnerable to changes in hormonal milieu. Thus, children are at greater risk of toxicant-related illnesses than adults. However, most data are collected from laboratory studies, and it remains to be determined that the levels of chemicals in the environment can impair human reproductive health. There is also significant genetic variability between human and animal species in their reactions to chemicals. The effects of low-dose, chronic, and multiple chemical exposures warrant further investigation in order to characterize the risk of environmental agents to humans. The aims of this review, which will focus on male reproduction, are to: 1) identify synthetic chemicals in the environment that fall into the ED class; 2) describe their mechanisms of toxicity in reproductive tissues; and, 3) outline the direction of future research efforts with respect to EDs.

Alexander FE. **Clusters and clustering of childhood cancer: a review**. European Journal of Epidemiology 1999;15(9):847-52.

Methodological considerations in the study of clusters and clustering of childhood cancer are reviewed briefly. A selection of 11 studies of individual clusters of childhood leukaemia which are either particularly notable or recent and have been reported in peer review journals is then considered. Focus is placed on sources of alerts, descriptive studies, field-work studies, conclusions and communication management. Some of these studies are probably essential but they are unlikely to yield firm conclusions; studies of large data sets are recommended. No causal factor has been identified which can explain a single cluster of childhood leukaemia.

Boffetta P, Tredaniel J, Greco A. **Risk of childhood cancer and adult lung cancer after childhood exposure to passive smoke: a meta-analysis.** Environmental Health Perspectives 2000 Jan;108(1):73-82.

We identified more than 30 studies on the association between exposure to maternal tobacco smoke during pregnancy and cancer in childhood. We combined their results in meta-analyses based on a random effects model. The results of the meta-analyses suggest a small increase in risk of all neoplasms [relative risk (RR) 1.10; 95% confidence interval (CI), 1.03-1.19; based on 12 studies], but not of specific neoplasms such as leukemia (RR 1.05; CI, 0.82-1.34; 8 studies) and central nervous system tumors (RR 1.04; CI, 0.92-1. 18; 12 studies). Results for other specific neoplasms were sparse, but the available data did not suggest a strong association for any type of tumor. No clear evidence of dose response was present in the studies that addressed this issue. The results on exposure to maternal tobacco smoke before or after pregnancy are too sparse to allow a conclusion. The results on exposure to paternal tobacco smoke suggest an association with brain tumors (RR 1.22; CI, 1.05-1. 40; based on 10 studies) and lymphomas (RR 2.08; CI, 1.08-3.98; 4 studies). The data are too sparse for the other neoplasms, although the results of a few recent large studies are compatible with a weak carcinogenic effect of paternal

smoke. For exposure from either maternal or paternal smoke, bias and confounding cannot yet be ruled out. Further studies are needed to confirm the hypothesis that parental tobacco smoke, from the father in particular, is a risk factor of childhood cancer. Results on the risk of lung cancer in adulthood and childhood passive smoking exposure are available from 11 studies: they do not provide evidence of an increased risk (summary RR 0.91; CI, 0.80-1.05).

Bolande RP. **Prenatal exposures and childhood cancer**. Pediatric and Developmental Pathology 1999;2(3):208-14.

No Abstract Available

Bove F, Shim Y, Zeitz P. **Drinking water contaminants and adverse pregnancy outcomes: a review**. Environmental Health Perspectives 2002;110:61-74.

Concern for exposures to drinking water contaminants and their effects on adverse birth outcomes has prompted several studies evaluating chlorination disinfection by-products and chlorinated solvents. Some of these contaminants are found to be teratogenic in animal studies. This review evaluates 14 studies on chlorination disinfection by-products such as trihalomethanes (THMs) and five studies on chlorinated solvents such as trichloroethylene (TCE). The adverse birth outcomes discussed in this review include small for gestational age (SGA), low birth weight, preterm birth, birth defects, spontaneous abortions, and fetal deaths. Because of heterogeneities across the studies in the characterization of birth outcomes, the assessment and categorization of exposures, and the levels and mixtures of contaminants, a qualitative review was conducted. Generally, the chief bias in these studies was exposure misclassification that most likely underestimated the risk, as well as distorted exposure-response relationships. The general lack of confounding bias by risk factors resulted from these factors not being associated with drinking water exposures. The studies of THMs and adverse birth outcomes provide moderate evidence for associations with SGA, neural tube defects (NTDs), and spontaneous abortions. Because fewer studies have been conducted for the chlorinated solvents than for THMs, the evidence for associations is less clear. Nevertheless, the findings of excess NTDs, oral clefts, cardiac defects, and choanal atresia in studies that evaluated TCE-contaminated drinking water deserve follow-up.

Bowman P, Oblender M, Oeffinger KC, Ward J. **Childhood cancer and environmental toxins: the debate continues**. Family & Community Health 2002 Jan;24(4):27-38.

Despite its rarity and advances in treatment and supportive care, cancer remains the leading cause of death from disease in children under 15. While the field of pediatric oncology has seen some advances in diagnostic and treatment techniques, researchers continue to face numerous hurdles in determining causative factors associated with childhood cancer. One of the most hotly contested issues in this area is the possible link between childhood cancer and environmental toxins. This article presents an interview with three pediatric oncologists and an environmental research toxicologist to help provide insight into the relationship between environmental exposures and childhood cancer.

Breier BH, Vickers MH, Ikenasio BA, Chan KY, Wong WPS. **Fetal programming of appetite and obesity**. Molecular and Cellular Endocrinology 2001 Dec 20; 185(1-2);73-79.

Obesity and related metabolic disorders are prevalent health issues in modern society and are commonly attributed to lifestyle and dietary factors. However, the mechanisms by which environmental factors modulate the physiological systems that control weight regulation and the aetiology of metabolic disorders, which manifest in adult life, may have their roots before birth. The 'fetal origins' or 'fetal programming' paradigm is based on the observation that environmental changes can reset the developmental path during intrauterine development leading to obesity and cardiovascular and metabolic disorders later in life. The pathogenesis is not based on genetic defects but on altered genetic expression as a consequence of an adaptation to environmental changes during fetal development. While many endocrine systems can be affected by fetal programming recent experimental studies suggest that leptin and insulin resistance are critical endocrine defects in the pathogenesis of programming-induced obesity and metabolic disorders. However, it remains to be determined whether postnatal obesity is a consequence of programming of appetite regulation and whether hyperphagia is the main underlying cause of the increased adiposity and the development of metabolic disorders.

Bremne JD, Vermetten E. **Stress and development: behavioral and biological consequences**. Developmental Psychopathology 2001 Summer;13(3):473-89.

Childhood abuse is an important public health problem; however, little is known about the effects of abuse on the brain and neurobiological development. This article reviews the behavioral and biological consequences of childhood abuse and places them in a developmental context. Animal studies show that both positive and negative events early in life can influence neurobiological development in unique ways. Early stressors such as maternal separation result in lasting effects on stress-responsive neurobiological systems, including the hypothalamic-pituitary-adrenal (HPA) axis and noradrenergic systems. These studies also implicate a brain area involved in learning and memory, the hippocampus. in the long-term consequences of early stress. Clinical studies of patients with a history of abuse also implicate dysfunction in the HPA axis and the noradrenergic and hippocampal systems; however, there are multiple questions related to chronicity of stress, developmental epoch at the time of the stressor, presence of stress-related psychiatric disorders including posttraumatic stress disorder and depression. and psychological factors mediating the response to trauma that need to be addressed in this field of research. Understanding the effects of abuse on the development of the brain and neurobiology will nevertheless have important treatment and policy implications.

Brenner RA, Overpeck MD, Trumble AC, DerSimonian R, Berendes H. **Deaths attributable to injuries in infants, United States, 1983-1991**. Pediatrics 1999 May;103(5 Pt 1):968-74

OBJECTIVE: To describe risk factors for injury death among infants in the United States by the specific external cause of death. METHODS: Data were analyzed from the US-linked birth/infant death files for the years 1983-1991. Potential risk factors for injury death were identified from birth certificate data and included both maternal and infant factors. Injury rates were calculated by external cause of death. Characteristics of infants who died from an injury were compared with those of the entire birth cohort. The independent effect of potential risk factors was assessed in multivariate analyses using a case-control study design. RESULTS: A total of 10 370 injury deaths were identified over the 9-year study period (29. 72/100 000 live births). The leading causes of death were homicide, suffocation, motor vehicle crashes, and

choking (inhalation of food or objects). There was no significant temporal trend in the overall rate of injury death; however, this was because significant increases in the rates of death from homicide (6.4%/year) and mechanical suffocation (3.7%/year) were offset by decreases in rates of death from fires (-4.7%/year) and choking (-4.6%/year). In adjusted analyses, infants born to mothers with no prenatal care, <12 years of education, two or more previous live births, Native American race, or <20 years of age were at twice the risk of injury death compared with the lowest risk groups (initiation of prenatal care in the first trimester, >/=16 years of education, no previous live births, white, or >/=25 years of age). When analyzed by the specific cause of death, the factors that were associated most strongly with death varied. For example, Native Americans were at greatest risk of a motor vehicle related death (compared with whites: OR: 3.6; 95% CI: 1.8-7.1), and infants with birth weights of <1500 g were at greatest risk of death attributable to inhalation of food (compared with >/=2500 g: OR: 9.6; 95% CI: 3.3-28.0) or objects (OR: 11.8; 95% CI: 4.5-30.5). CONCLUSION: A number of sociodemographic characteristics are associated with an increased risk of injury-related death in infants. The strength of associations between specific risk factors and death varies with the external cause of death, thus identifying high-risk subgroups for targeting of cause-specific interventions and simultaneously increasing our understanding of the individual and societal mechanisms underlying these tragedies.

Carpenter DO. **Effects of metals on the nervous system of humans and animals**. International Journal of Occupational Medicine and Environmental Health 2001;14(3):209-18.

Several metals have toxic actions on nerve cells and neurobehavorial functioning. These toxic actions can be expressed either as developmental effects or as an increased risk of neurodegenerative diseases in old age. The major metals causing neurobehavioral effects after developmental exposure are lead and methylmercury. Lead exposure in young children results in a permanent loss of IQ of approximately 5 to 7 IQ points, and also results in a shortened attention span and expression of anti-social behaviors. There is a critical time period (<2 years of age) for development of these effects, after which the effects do not appear to be reversible even if blood lead levels are lowered with chelation. Methylmercury has also been found to have effects on cognition at low doses, and prenatal exposure at higher levels can disrupt brain development. Metals have also been implicated in neurodegenerative diseases, although it is unlikely that they are the sole cause for any of them. Elevated aluminum levels in blood, usually resulting from kidney dialysis at home with well water containing high aluminum, result in dementia that is similar to but probably different from that of Alzheimer's disease. However, there is some epidemiological evidence for elevated risk of Alzheimer's in areas where there is high concentration of aluminum in drinking water. Other metals, especially lead, mercury, manganese and copper, have been implicated in amvotrophic lateral sclerosis and Parkinson's disease.

Caspi A, Taylor A, Moffitt TE. **Neighborhood deprivation affects children's mental health: environmental risks identified in a genetic design**. Psychological Science 2000 Jul;11(4):338-42.

The possibility that neighborhood conditions affect children's development has captured much attention because of its implications for prevention. But does growing up in deprived neighborhoods matter above and beyond a genetic liability to behavior problems, if genetically vulnerable families tend to concentrate in poor neighborhoods? A nationwide study of 2-year-old twins shows that children in deprived neighborhoods were at increased risk for emotional and

behavioral problems over and above any genetic liability. Environmental factors shared by members of a family accounted for 20% of the population variation in children's behavior problems, and neighborhood deprivation accounted for 5% of this family-wide environmental effect. The results suggest that the link between poor neighborhoods and children's mental health may be a true environmental effect, and demonstrate that genetic designs are environmentally informative and can be used to identify modifiable risk factors for promoting child health.

Cohen HEA, Sheldon LS, Burke JM, McCurdy TR, Berry MR, Rigas ML, et al. **Children's exposure assessment: a review of factors influencing children's exposure, and the data available to characterize and assess that exposure**. Environmental Health Perspectives 2000;108(6):475-86.

We review the factors influencing children's exposure to environmental contaminants and the data available to characterize and assess that exposure. Children's activity pattern data requirements are demonstrated in the context of the algorithms used to estimate exposure by inhalation, dermal contact, and ingestion. Currently, data on children's exposures and activities are insufficient to adequately assess multimedia exposures to environmental contaminants. As a result, regulators use a series of default assumptions and exposure factors when conducting exposure assessments. Data to reduce uncertainty in the assumptions and exposure estimates are needed to ensure chemicals are regulated appropriately to protect children's health. To improve the database, advancement in the following general areas of research is required: identification of appropriate age/developmental benchmarks for categorizing children in exposure assessment; development and improvement of methods for monitoring children's exposures and activities; collection of activity pattern data for children (especially young children) required to assess exposure by all routes; collection of data on concentrations of environmental contaminants, biomarkers, and transfer coefficients that can be used as inputs to aggregate exposure models.

Cummins SK, Jackson RJ. **The built environment and children's health**. Pediatric Clinics of North America 2001 Oct;48(5):1241-52.

The built environment embraces a wide range of concepts, from the design and integrity of housing, to land-use urban planning. A high-quality environment is essential for children to achieve optimal health and development. Building and land-use policies, including the quality and design of a child's physical environment, can cause or prevent illness, disability, and injury, and can degrade or preserve natural resources. Though many common pediatric conditions such as obesity, asthma, and lead poisoning, as well as injuries, are associated with risk factors within a child's built environment, this issue has received little attention from researchers or policymakers. This new field is ripe for etiologic and prevention research, and we need pediatric advocates to speak out for children's needs within this arena.

Denson KWE. **Passive smoking in infants, children and adolescents. The effects of diet and socioeconomic factors**. International Archives of Occupational and Environmental Health 2001;74(8):525-32.

Objectives: Many studies have associated environmental tobacco smoke (ETS) exposure with an increased risk for various diseases in infants and children, and although superficially the evidence is compelling, on closer scrutiny socioeconomic factors, especially diet, could have a

greater contributory effect. An analysis of this evidence was made. Results: Studies which have correlated smoking during pregnancy with low birth weight have considered weight gain and cholesterol levels as a measure of nutrition in the mother, but not the micronutrient content of the diet to which low birth weights could be due. Several authors have attributed ETS exposure to the presence of abnormal lipid profiles in children and adolescents, without considering the diet of the latter, and the abnormal lipids have been linked to a subsequent increased risk for atherosclerosis. The evidence linking lower respiratory infections and bronchitis with passive smoking is strong, although it seems likely that the diet of the mother during pregnancy or breast feeding is equally important. Similarly, increased risks for asthma, otitis media and sudden infant death syndrome have been attributed to the effects of passive smoking, without adequate allowance for confounding by other socioeconomic factors. Conclusion: After consideration of the accumulated evidence, it seems improbable that the small exposure could produce all of the effects claimed.

Douwes J, Pearce N, Heederik D. **Does environmental endotoxin exposure prevent asthma?** Thorax 2002 Jan;57(1):86-90**.**

The evidence as to whether exposure to environmental airborne endotoxin plays a protective or an inducing role in the development of asthma is reviewed. Studies of endotoxin and atopy, endotoxin and asthma, and farming and asthma are considered and, in each instance, a distinction is made between evidence of primary causation and evidence of secondary causation. It is concluded that, although it is plausible that bacterial endotoxin may protect against the development of asthma, there is considerable reason for caution regarding this hypothesis.

Eggleston PA, Buckley TJ, Breysse PN, Wills-Karp M, Kleeberger SR, Jaakkola JJ. **The environment and asthma in U.S. inner cities**. Environmental Health Perspectives 1999 Jun;107 Suppl 3:439-50.

The prevalence and severity of asthma has increased in the last 20 years, and the greatest increase has been seen among children and young adults living in U.S. inner cities. The reasons for this increase are obviously complex, but include environmental exposures to allergens and pollutants, changing patterns of medication, and the psychosocial stresses of living in poor inner-city neighborhoods. This paper presents an overview of environmental, immunologic, and genetic factors associated with asthma morbidity and mortality. This overview can be used to provide a framework for designing an interdisciplinary research program to address the complexities of asthma etiology and exacerbation. The strongest epidemiologic association has been found between asthma morbidity and the exposure of immunologically sensitive asthmatic patients to airborne allergens. Our current understanding of the process of sensitization suggests that there is a strong genetic predisposition to form IgE to allergenic proteins on airborne particles. Much of this work has been conducted with animal models, but in a number of instances, specific confirmation has been reported in humans. Sensitized individuals respond to inhaled exposure with immediate mast-cell dependent inflammation that may be augmented by pollutant particles, especially diesel exhaust particles. Relatively little is known about the methods of assessing exposure to airborne pollutants, especially biologically active particulates. However, to examine the relationship of morbidity in genetically predisposed individuals, it will be important to determine the most relevant method of making this assessment.

Eskenazi B, Castorina R. **Association of prenatal maternal or postnatal child environmental tobacco smoke exposure and neurodevelopmental and behavioral problems in children**. Environmental Health Perspectives 1999 Dec;107(12):991-1000.

We review the potential neurodevelopmental and behavioral effects of children's prenatal and/or postnatal exposure to environmental tobacco smoke (ETS). Children's exposure to ETS has been assessed in epidemiologic studies as a risk factor for a variety of behavioral and neurodevelopmental problems including reduced general intellectual ability, skills in language and auditory tasks, and academic achievement, and behavioral problems such as hyperactivity and decreased attention spans. We review 17 epidemiologic studies that have attempted to separate the effects of maternal active smoking during pregnancy from passive ETS smoke exposure by the pregnant mother or the child. Based on the available data, we found that ETS exposure could cause subtle changes in children's neurodevelopment and behavior. However, studies to date are difficult to interpret because of the unknown influence of uncontrolled confounding factors, imprecision in measurements of smoking exposure, and collinearity of pre- and postnatal maternal smoking. Although some evidence suggests that maternal smoking during pregnancy may be associated with deficits in intellectual ability and behavioral problems in children, the impact of prenatal or postnatal.

Feeley M, Brouwer A. **Health risks to infants from exposure to PCBs, PCDDs and PCDFs**. Food Additives and Contaminants 2000 Apr;17(4):325-33.

Global contamination by a variety of anthropogenic persistent organic chemicals, such as dioxins and PCBs, has resulted in human exposure throughout all phases of development. Detectable concentrations of PCBs and dioxins have been found in amniotic fluid, placenta and foetal tissue samples while infants who are breast-fed can obtain blood levels greater than those of their mother's. In two separate food poisoning episodes where infants were exposed in utero to elevated levels of heat-degraded PCBs (PCBs, PCQs, PCDFs), a variety of adverse mental and physical developmental abnormalities have been observed. In additional human cohorts where exposure could be considered as environmental or background, more subtle effects, including lower birth weights, alterations in thyroid hormones and lymphocyte subpopulations and detriments in neurological development, have been consistently seen. In most instances, negative associations were made between in utero exposure to contaminants compared with lactational. Although the observed neurodevelopmental deficits have been described as subtle, there could be unknown consequences related to future intellectual functionality. Current regulatory efforts should focus on identification and control of environment and food chain contamination as in utero exposure is a direct consequence of the accumulated maternal body burdens.

Gitterman BA, Bearer CF. **A developmental approach to pediatric environmental health**. Pediatric Clinics of North America 2001 Oct;48(5):1071-83.

Children cannot be considered "little adults" in the field of environmental medicine. There are differences in exposures, pathways of absorption, tissue distribution, ability to biotransform or eliminate chemicals from the body, and responses to chemical and radiation. The differences vary with the developmental stages of the child. Children all respond differently to environmental toxicants. Knowledge, although rapidly increasing, is still incomplete regarding the impact of the environment on children. As health care providers, prevention is an ally but must be approached differently at each stage of a child's life.

Glaser D. **Child abuse and neglect and the brain: a review.** Journal of Child Psychology and Psychiatry 2000 Jan;41(1):97-116.

Developmental psychology and the study of behaviour and emotion have tended to be considered in parallel to the study of neurobiological processes. This review explores the effects of child abuse and neglect on the brain, excluding nonaccidental injury that causes gross physical trauma to the brain. It commences with a background summary of the nature, context, and some deleterious effects of omission and commission within child maltreatment. There is no post-maltreatment syndrome, outcomes varying with many factors including nature, duration, and interpersonal context of the maltreatment as well as the nature of later intervention. There then follows a section on environmental influences on brain development, demonstrating the dependence of the orderly process of neurodevelopment on the child's environment. Ontogenesis, or the development of the self through self-determination, proceeds in the context of the nature-nurture interaction. As a prelude to reviewing the neurobiology of child abuse and neglect, the next section is concerned with bridging the mind and the brain. Here, neurobiological processes, including cellular, biochemical, and neurophysiological processes, are examined alongside their behavioural, cognitive, and emotional equivalents and vice versa. Child maltreatment is a potent source of stress and the stress response is therefore discussed in some detail. Evidence is outlined for the buffering effects of a secure attachment on the stress response. The section dealing with actual effects on the brain of child abuse and neglect discusses manifestations of the stress response including dysregulation of the hypothalamic-pituitary-adrenal axis, and parasympathetic and catecholamine responses. Recent evidence about reduction in brain volume following child abuse and neglect is also outlined. Some biochemical, functional, and structural changes in the brain that are not reflections of the stress response are observed following child maltreatment. The mechanisms bringing about these changes are less clearly understood and may well be related to early and more chronic abuse and neglect affecting the process of brain development. The behavioural and emotional concomitants of their neurobiological manifestations are discussed. The importance of early intervention and attention to the chronicity of environmental adversity may indicate the need for permanent alternative caregivers, in order to preserve the development of the most vulnerable children.

Gold DR. **Environmental tobacco smoke, indoor allergens, and childhood asthma.** Environmental Health Perspectives 2000 Aug;108 Suppl 4:643-51.

Both environmental tobacco smoke and indoor allergens can exacerbate already established childhood albeit primarily through quite disparate mechanisms. In infancy and childhood, environmental tobacco smoke (ETS) exposure is associated with measures of decreased flow in the airways, bronchial hyperresponsiveness, and increased respiratory infections, but the relationship between ETS and allergy is poorly understood. Indoor allergens from dust mite, cockroach, and cat can be associated with asthma exacerbation in children sensitized to the specific allergens. The precise role of either ETS or indoor allergens in the development of asthma is less well understood. The strong and consistent association between ETS and asthma development in young children may relate to both prenatal and postnatal influences on airway caliber or bronchial responsiveness. Dust mite allergen levels predict asthma in children sensitized to dust mite. The tendency to develop specific IgE antibodies to allergens (sensitization) is associated with and may be preceded by the development of a T-helper (Th)2 profile of cytokine release. The importance of either ETS or indoor allergens in the

differentiation of T cells into a Th2-type profile of cytokine release or in the localization of immediate-type allergic responses to the lung is unknown. This article evaluates the strength of the evidence that ETS or indoor allergens influence asthma exacerbation and asthma development in children. We also selectively review data for the effectiveness of allergen reduction in reducing asthma symptoms and present a potential research agenda regarding these two broad areas of environmental exposure and their relationship to childhood asthma.

Goldsmith CA, Kobzik L. **Particulate air pollution and asthma: a review of epidemiological and biological studies**. Reviews on Environmental Health 1999 Jul-Sep;14(3):121-34.

The link between exposure to air pollution and exacerbation of asthma symptoms has been investigated by epidemiological study and by direct biological experimentation. In asthmatics, epidemiological studies generally show a positive correlation between the particulate fraction of air pollution and increased morbidity, although roles for other co-pollutants (for example, ozone) are implicated as well. Direct experimentation using air pollutants, especially particles, to investigate their effects on humans or on animal models of asthma provides corroboration of the epidemiology and has begun to identify the pathophysiological mechanisms involved. We begin this review with an overview of air pollution, followed by a survey of the epidemiological and experimental data regarding air pollution particles and asthma. We finish with a discussion of directions for future research.

Gressens P, Mesples B, Sahir N, Marret S, Sola A. **Environmental factors and disturbances of brain development**. Seminars in Neonatology 2001;6(2):185-94.

Foetal and neonatal brain is under the influence of environmental factors from maternal and extra-maternal origin. Based on the available data, these environmental factors can be classified into three arbitrary groups: (i) factors and maternal status with a demonstrated deleterious effect on the foetal brain (i.e. ethanol, cocaine, some drugs including anticonvulsants, some viral infections, maternal diabetes, untreated maternal phenylketonuria); (ii) factors highly suspected to interfere with foetal brain development (i.e. lead and other heavy metals, some drugs like benzodiazepines, nicotine); (iii) factors which have been shown to be safe for the developing brain in the available studies (i.e. low to moderate doses of caffeine, methadone). However, most of these studies do not address the potential risk of environmental factors on minimal to moderate cognitive and behavioural disturbances. Finally, the impact of the neonatal environment on brain development in very pre-term infants is probably underestimated.

Grossman DC. **The history of injury control and the epidemiology of child and adolescent injuries**. The Future of Children 2000;10(1):23-52.

Unintentional injuries claim the lives of more children each year than any other cause of death. A substantial proportion of child hospitalizations and emergency department visits also are attributable to unintentional injuries. The conceptualization of unintentional injuries as a public health problem that is preventable has gained credibility over the past few decades, as effective solutions to reduce the burden of injuries--such as child safety seats, bicycle helmets, and smoke detectors--have been identified. Successful implementation of these strategies requires a clear understanding of the circumstances surrounding injuries and the risk and protective factors that influence the likelihood that a child will be injured. Although adequate data on these factors is available for some causes of injury, such as motor vehicle crashes, it is almost nonexistent for

others, such as unintentional firearm injuries. Overall, unintentional injury rates are highest among adolescents ages 15 to 19, males, children from impoverished families, and minorities. Also, some injuries occur more often in rural areas. Although these demographic risk factors cannot be modified, environmental and behavioral risks, such as unsafe roads, alcohol intoxication, unfenced swimming pools, and the absence of a smoke detector in the home, can be modified successfully with appropriate strategies. Motor vehicle occupant, drowning, and pedestrian injuries were the most common unintentional injuries causing death among children ages 0 to 19 in 1996. Together, these mechanisms accounted for more than half of all unintentional injury deaths among children and adolescents, although rates varied considerably by age. Child injury death rates across most age categories and mechanisms of injury have declined during the past 20 years, yet the reasons for these declines are poorly understood. Additional research about risk and protective factors, and efforts to implement successful injury prevention strategies among populations at highest risk for injuries, are necessary to further reduce the toll on children's lives.

Kilpelainen M, Terho EO, Helenius H, Koskenvuo M**. Farm environment in childhood prevents the development of allergies**. Clinical and Experimental Allergy 2000 Feb;30(2):201-8.

BACKGROUND: A protective effect of infections in early life might explain the firmly reported finding of an inverse association between atopic disorders and large sibships. OBJECTIVE: To study the effect of childhood farm, rural non-farm and urban environment, as well as family size and other factors on the occurrence of asthma, wheezing and atopic disorders up to young adulthood. METHODS: Data on lifetime prevalence of physician-diagnosed asthma, allergic rhinitis and/or allergic conjunctivitis, atopic dermatitis, as well as self-reported episodic wheezing from 10 667 Finnish first-year university students aged 18-24 years were collected by a postal questionnaire. Associations of lifetime prevalence of the diseases with living on a farm, in a rural non-farm and urban environment during childhood were estimated by logistic regression analysis. Adjustment was made for potential confounding by gender, parental atopy, parental education, number of older siblings, day care outside the home and passive smoking. RESULTS: The childhood farm environment independently reduced the risk for physician-diagnosed allergic rhinitis and/or allergic conjunctivitis (adjusted odds ratio 0.63, 95% CI 0.50-0.79, $P < 0.001$), and for diagnosed asthma and episodic wheezing analysed together (OR 0.71, 95% CI 0.54-0.93, $P < 0.05$), but not for atopic dermatitis during lifetime. Urban childhood environment did not show independent increased risk when compared with rural non-farm residence. The inverse association of sibship size with the occurrence of allergic rhinitis and/or allergic conjunctivitis was found among subjects with one (OR 0.86, 95% CI 0.77-0.96, $P < 0.01$) or at least four older siblings (OR 0.47, 95% CI 0.26-0.84, $P < 0.05$). CONCLUSION: Childhood farm environment seems to have a protective effect against allergic rhinitis and/or conjunctivitis, and more weakly against asthma and wheezing irrespective of family size. Environmental exposure to immune modulating agents, such as environmental mycobacteria and actinomycetes, favouring manifestation of a nonatopic phenotype could explain the finding.

Laflamme L. **Pupil injury risks as a function of physical and psychosocial environmental problems experienced at school**. Journal of the International Society for Child and Adolescent Injury Prevention 2001 Jun;7(2):146-9.

OBJECTIVES: To investigate relations between physical and psychosocial environmental problems in schools, as perceived by school principals, and injuries among pupils. METHOD: Proportionate injury ratios (PIRs) were computed for 77 public sector Swedish schools (33,248 pupils), and divided into four classes based on types of environmental problems reported. Sports related injuries, injuries during recesses, and violence related injuries were considered. RESULTS: The schools reporting psychosocial problems (9.1% of schools and 7.3% of pupils) had more injuries than expected by chance than all types of injuries aggregated (PIR = 1.92; 95% confidence interval (CI) 1.64 to 2.27), and in the case of sports related injuries (PIR = 1.79; 95% CI 1.37 to 2.34) and injuries due to physical violence (PIR = 2.20; 95% CI 1.33 to 3.65). There were no significant excess risks of injuries for schools facing physical problems or a combination of physical and psychosocial problems. CONCLUSIONS: Psychosocial problems may exacerbate the risk of intentional and unintentional injuries among pupils. The results offer a reminder that school environment must be planned as part of any assessment of youth safety.

Landrigan PJ. **Children's environmental health. Lessons from the past and prospects for the future**. Pediatric Clinics of North America 2001;48(5):1319-30.

Environmental pediatrics is an area of pediatric medicine that has come a long way in the past 50 years. It has risen to importance in parallel with two developments: (1) the conquest in the industrialized nations of the major infectious diseases and their replacement by chronic conditions, such as asthma, cancer, developmental disabilities, and birth defects as the primary causes of illness and death in children and (2) the growing recognition that chemicals in the environment are responsible, at least in part, for these changes in patterns of disease. The challenge now to environmental pediatrics is to better understand the impact of chemical substances on the patterns of health and disease in children and to design evidence-based approaches to the treatment and prevention of childhood disease of environmental origin.

Lanphear BP, Kahn RS, Berger O, Auinger P, Bortnick SM, Nahhas RW. **Contribution of residential exposures to asthma in us children and adolescents**. Pediatrics 2001 Jun;107(6): E98.

Residential exposures are recognized risk factors for asthma, but the relative contribution of specific indoor allergens and their overall contribution to asthma among older children and adolescents in the United States are unknown. OBJECTIVE: To estimate the relative contributions, population-attributable risks, and costs of residential risk factors for doctor-diagnosed asthma. Design. Nationally representative, cross-sectional survey conducted from 1988 to 1994. SETTING AND PARTICIPANTS: A total of 5384 children who were 6 to 16 years old and participated in the National Health and Nutrition Examination Survey III, a survey of the health and nutritional status of children and adults in the United States. MAIN OUTCOME MEASURE: Doctor-diagnosed asthma, as reported by the parent. RESULTS: Five hundred three of 5384 children and adolescents (11.4%) had doctor-diagnosed asthma. After adjusting for age, gender, race, urban status, region of country, educational attainment of the head of household, and poverty, predictors of doctor-diagnosed asthma included a history of allergy to a pet (odds ratio [OR: 2.4; 95% confidence interval [CI]: 1.7, 3.3), presence of a pet in the household (OR: 1.5; 95% CI: 1.1, 2.1), and immediate hypersensitivity to dust mite (OR: 1.5; 95% CI: 1.05, 2.0), Alternaria (OR: 1.9; 95% CI: 1.3, 2.8), and cockroach allergens (OR: 1.4; CI: 1.04, 1.9). Family history of atopy (OR: 1.7; 95% CI: 1.1, 2.7) and diagnosis of allergic rhinitis (OR: 2.1; CI: 1.1, 3.7) were also predictors for asthma. The population-attributable risk of having

1 or more residential exposures associated with doctor-diagnosed asthma was 44.4% (95% CI: 29-60), or an estimated 2 million excess cases. The attributable cost of asthma resulting from residential exposures was $405 million (95% CI: $264-$547 million) annually. CONCLUSIONS: The elimination of identified residential exposures, if causally associated with asthma, would result in a 44% decline in doctor-diagnosed asthma among older children and adolescents in the United States.

London EA, Etzel RA. **The environment as an etiologic factor in autism: a new direction for research**. Environmental Health Perspectives 2000 Jun;108 Suppl 3:401-4.

Autism is one of a group of developmental disorders that have devastating lifelong effects on its victims. Despite the severity of the disease and the fact that it is relatively common (15 in 10,000), there is still little understanding of its etiology. Although believed to be highly genetic, no abnormal genes have been found. Recent findings in autism and in related disorders point to the possibility that the disease is caused by a gene-environment interaction. Epidemiologic studies indicate that the number of cases of autism is increasing dramatically each year. It is not clear whether this is due to a real increase in the disease or whether this is an artifact of ascertainment. A new theory regarding the etiology of autism suggests that it may be a disease of very early fetal development (approximately day 20-24 of gestation). This theory has initiated new lines of investigation into developmental genes. Environmental exposures during pregnancy could cause or contribute to autism based on the neurobiology of these genes.

McConnell R, Berhane K, Gilliland F, London SJ, Islam T, Gauderman WJ, et al. **Asthma in exercising children exposed to ozone: a cohort study**. Lancet 2002 Feb 2;359(9304):386-91.

BACKGROUND: Little is known about the effect of exposure to air pollution during exercise or time spent outdoors on the development of asthma. We investigated the relation between newly-diagnosed asthma and team sports in a cohort of children exposed to different concentrations and mixtures of air pollutants. METHODS: 3535 children with no history of asthma were recruited from schools in 12 communities in southern California and were followed up for up to 5 years. 265 children reported a new diagnosis of asthma during follow-up. We assessed risk of asthma in children playing team sports at study entry in six communities with high daytime ozone concentrations, six with lower concentrations, and in communities with high or low concentrations of nitrogen dioxide, particulate matter, and inorganic-acid vapour. FINDINGS: In communities with high ozone concentrations, the relative risk of developing asthma in children playing three or more sports was 3.3 (95% CI 1.9-5.8), compared with children playing no sports. Sports had no effect in areas of low ozone concentration (0.8, 0.4-1.6). Time spent outside was associated with a higher incidence of asthma in areas of high ozone (1.4, 1.0-2.1), but not in areas of low ozone. Exposure to pollutants other than ozone did not alter the effect of team sports. INTERPRETATION: Incidence of new diagnoses of asthma is associated with heavy exercise in communities with high concentrations of ozone, thus, air pollution and outdoor exercise could contribute to the development of asthma in children.

Nevin R. **How lead exposure relates to temporal changes in IQ, violent crime, and unwed pregnancy**. Environmental Research 2000 May;83(1):1-22.

This study compares changes in children's blood lead levels in the United States with subsequent changes in IQ, based on norm comparisons for the Cognitive Abilities Test (CogAT) given to

representative national samples of children in 1984 and 1992. The CogAT norm comparisons indicate shifts in IQ levels consistent with the blood lead to IQ relationship reported by an earlier study and population shifts in average blood lead for children under age 6 between 1976 and 1991. The CogAT norm comparisons also support studies indicating that the IQ to blood lead slope may increase at lower blood lead levels. Furthermore, long-term trends in population exposure to gasoline lead were found to be remarkably consistent with subsequent changes in violent crime and unwed pregnancy. Long-term trends in paint and gasoline lead exposure are also strongly associated with subsequent trends in murder rates going back to 1900. The findings on violent crime and unwed pregnancy are consistent with published data describing the relationship between IQ and social behavior. The findings with respect to violent crime are also consistent with studies indicating that children with higher bone lead tend to display more aggressive and delinquent behavior. This analysis demonstrates that widespread exposure to lead is likely to have profound implications for a wide array of socially undesirable outcomes.

Peden DB. **Development of atopy and asthma: candidate environmental influences and important periods of exposure**. Environmental Health Perspectives 2000 Jun;108 Suppl 3:475-82.

Atopy is a major risk factor for the development of asthma. Immune processes that lead to the development of antigen-specific IgE are essential to the development of atopy. This review examines the immune processes that are candidate targets for modulation by environmental agents; environmental and lifestyle factors that have been suggested as modulators of the development of atopy; and the impact of known environmental agents on atopic processes in the airway. The most important periods of immune development with regard to expression of atopy are likely during gestation and early childhood. A better understanding of which environmental agents are important, as well as the period of life during which these agents may exert an important effect, is essential to devising rational environmental avoidance strategies for at-risk populations.

Pereira LAA, Loomis D, Conceicao GMS, Braga ALF, Arcas RM, Kishi HS, et al. **Association between air pollution and intrauterine mortality in Sao Paulo, Brazil**. Environmental Health Perspectives 1998 Jun;106(6):325-29.

The associations among daily counts of intrauterine mortality and pollutant concentrations (NO2, SO2, CO, O3, and particulate matter ltoreq10 mum) were investigated for the period ranging from January 1991 to December 1992 in the city of Sao Paulo, Brazil. We used Poisson regression techniques, adjusted for season and weather. The association between intrauterine mortality and air pollution was strong for NO2 (coefficient = 0.0013/mug/m3; $p<0.01$) but lesser for SO2 (coefficient = 0.0005/mug/m3; $p<0.10$) and CO (coefficient = 0.0223/ppm; $p <0.10$). A significant association was observed when an index that combined these three pollutants was considered in the models instead of considering each pollutant individually ($p<0.01$). These associations exhibited a short time lag, not over 5 days. In addition, some evidence of fetal exposure to air pollution was obtained by disclosing a significant association between the levels of carboxyhemoglobin of blood sampled from the umbilical cord and ambient CO levels in children delivered by nonsmoking pregnant women in the period from May to July 1995. Our results suggest that air pollution in Sao Paulo may promote adverse health effects on fetuses.

Perera FP, Illman SM, Kinney PL, Whyatt RM, Kelvin EA, Shepard P, et al. **The challenge of preventing environmentally related disease in young children: community-based research in New York City**. Environmental Health Perspectives 2002;110(2):197-204.

Rates of developmental and respiratory diseases are disproportionately high in underserved, minority populations such as those in New York City's Washington Heights, Harlem, and the South Bronx. Blacks and Latinos in these neighborhoods represent high risk groups for asthma, adverse birth outcomes, impaired developments, and some types of cancer. The Columbia Center for Children's Environmental Health in Washington Heights uses molecular epidemiologic methods to study the health effects of urban indoor and outdoor air pollutants on children, prenatally and postnatally, in a cohort of over 500 African-American and Dominican (originally from the Dominican Republic) mothers and newborns. Extensive data are collected to determine exposures to particulate matter < 2.5 mum in aerodynamic diameter (PMSUB2.5), polycyclic aromatic hydrocarbons (PAHs), diesel exhaust particulate (DEP), nitrogen oxide, nonpersistent pesticides, home allergens (dust mite, mouse, cockroach), environmental tobacco smoke (ETS), and lead and other metals. Biomarkers, air sampling, and clinical assessments are used to study the effects of these exposures on children's increased risk for allergic sensitization, asthma and other respiratory disorders, impairment of neurocognitive and behavioral development, and potential cancer risk. The center conducts its research and community education in collaboration with 10 community-based health and environmental advocacy organizations. This unique academic-community partnership helps to guide the center's research so that it is most relevant to the context of the low-income, minority neighborhoods in which the cohort resides, and information is delivered back to these communities in meaningful ways. In turn, communities become better equipped to relay environmental health concerns to policy makers. In this paper we describe the center's research and its academic-community partnership and present some preliminary findings.

Reigart JR, Roberts JR. **Pesticides in children**. Pediatric Clinics of North America 2001 Oct; 48(5):1185-98.

Children are exposed to a wide range of pesticides, including insecticides, herbicides, fungicides, and rodenticides. They differ from adults in their exposures and responses to exposures. Acute and chronic toxicity are discussed, and important chronic effects, such as carcinogenesis, endocrine disruption, and neurodevelopment effects are reviewed. The state of laws and regulations are also discussed. Recommendations are made to pediatricians regarding treatment and advising families regarding avoidance of pesticide exposures and their effects.

Ross JA, Swensen AR. **Prenatal epidemiology of pediatric tumors**. Current Oncology Reports 2000 May;2(3):234-41.

With the exception of a small percentage of cases attributable to hereditary cancer syndromes (eg, familial retinoblastoma) or genetic syndromes (Down syndrome), the etiology of most childhood cancers is unknown. Recent epidemiologic studies have focused on the prenatal period and have investigated potential associations with parental age, cigarette smoking, birth weight of the child, parental occupational exposures, and specific environmental exposures. The following challenges lie ahead for future epidemiologic studies of childhood cancer: 1) improvement of diagnostic classification; 2) improved methods for exposure assessment; 3) evaluation of data

from molecular biology to generate biologically derived hypotheses; and 4) incorporation of markers of genetic susceptibility when feasible.

Rubin CH, Niskar AS. **Endocrine disruptors: an emerging environmental health problem**. Journal of the Medical Association of Georgia 1999 Dec;88(4):27-30.

No Abstract Available

Schuz J, Grigat JP, Brinkmann K, Michaelis J. **Residential magnetic fields as a risk factor for childhood acute leukaemia: results from a German population-based case-control study**. International Journal of Cancer 2001;91(5):728-35.

Our objective was to investigate whether exposure to residential power-frequency (50 Hz) magnetic fields above 0.2 microT increases a child's risk of leukaemia and to confirm or reject a finding from a previous German study on this topic, which reported increased leukaemia risk with exposure to stronger magnetic fields during the night. A population-based case-control study was used, covering the whole of the former West Germany. Residential magnetic fields were measured over 24 hr for 514 children with acute leukaemia identified by the German Childhood Cancer Registry and 1,301 control children taken from population registration files. Magnetic fields above 0.2 microT were relatively rare in Germany (only 1.5% of the study population). Childhood leukaemia and 24 hr median magnetic fields were only weakly related (OR = 1.55, 95% CI 0.65-3.67). A significant association was seen between childhood leukaemia and magnetic field exposure during the night (OR = 3.21, 95% CI 1.33-7.80). A dose-response-relationship was observed after combining the data of all German studies on magnetic fields and childhood leukaemia. The evidence for an association between childhood leukaemia and magnetic field exposure in our study comes from a measure of exposure during the night. Despite the large size of our study, the results are based on small numbers of exposed children. If the observed association stands, the effect on a population level in Germany would be small.

Solomon GM, Schettler T. **Environment and health: 6. Endocrine disruption and potential human health implications**. Canadian Medical Association Journal 2000 Nov 28;163(11):1471-6.

No Abstract Available

Sovikova E. **Environmental risk factors in mental development of children**. Toxicology Letters 2000;116:72.

No Abstract Available

Tickner JA, Schettler T, Guidotti T, McCally M, Rossi M. **Health risks posed by use of Di-2-ethylhexyl phthalate (DEHP) in PVC medical devices: a critical review**. American Journal of Industrial Medicine 2001;39(1):100-11.

BACKGROUND: Polyvinyl chloride plastics (PVC), made flexible through the addition of di-2-ethylhexyl phthalate (DEHP), are used in the production of a wide array of medical devices. From the late 1960s, leaching of DEHP from PVC medical devices and ultimate tissue deposition have been documented. METHODS: A critical review of DEHP exposure, metabolism, and toxicity data from human and animals studies was undertaken. A brief analysis

of alternatives to DEHP-plasticized PVC for use in medical device manufacture was completed. RESULTS: DEHP leaches in varying concentrations into solutions stored in PVC medical devices. Certain populations, including dialysis patients and hemophiliacs may have long-term exposures to clinically important doses of DEHP, while others, such as neonates and the developing fetus, may have exposures at critical points in development. In vivo and in vitro research links DEHP or its metabolites to a range of adverse effects in the liver, reproductive tract, kidneys, lungs, and heart. Developing animals are particularly susceptible to effects on the reproductive system. Some adverse effects in animal studies occur at levels of exposure experienced by patients in certain clinical settings. DEHP appears to pose a relatively low risk of hepatic cancer in humans. However, given lingering uncertainties about the relevance of the mechanism of action of carcinogenic effects in rodents for humans and interindividual variability, the possibility of DEHP-related carcinogenic responses in humans cannot be ruled out. CONCLUSIONS: The observed toxicity of DEHP and availability of alternatives to many DEHP-containing PVC medical devices presents a compelling argument for moving assertively, but carefully, to the substitution of other materials for PVC in medical devices. The substitution of other materials for PVC would have an added worker and community health benefit of reducing population exposures to DEHP, reducing the creation of dioxin from PVC production and disposal, and reducing risks from vinyl chloride monomer exposure.

Wadhwa PD, Sandman CA, Garite TJ. **The neurobiology of stress in human pregnancy: implications for prematurity and development of the fetal central nervous system**. Progress Brain Research 2001;133:131-42.

Adverse early experience, including prenatal maternal psychosocial stress, has the potential to negatively influence developmental processes through both physiological and behavioral mechanisms. This in turn may have adverse consequences for the mental and physical health, well-being and aging of the individual throughout the entire life-span. We have initiated a program of research on humans to examine the consequences of maternal stress and related factors in pregnancy on the length of gestation, fetal growth, and brain development. We have also investigated the physiological mechanisms that are involved. In this chapter we outline the theoretical rationale for this work and give an overview of our findings to date. These findings support a significant and independent role for behavioral processes such as maternal prenatal stress in the etiology of prematurity-related outcomes, and suggest that these effects are mediated, in part, by the maternal-placental-fetal neuroendocrine axis; specifically by placental corticotropin-releasing hormone. Using a fetal challenge paradigm as a novel method for quantifying fetal neurologic maturity in utero, we have found that the maternal environment exerts a significant influence on the fetal autonomic nervous system and on central nervous system processes related to recognition, memory and habituation. Finally, our findings provide preliminary evidence to support the notion that the influence of prenatal stress and maternal-placental hormones on the developing fetus may persist after birth, as assessed by measures of temperament and behavioral reactivity in the first 3 years of postnatal life. The implications of these studies for life-span development and health are discussed.

Wasserman GA, Liu X, Pine DS, Graziano JH. **Contribution of maternal smoking during pregnancy and lead exposure to early child behavior problems**. Neurotoxicology and Teratology 2001;23(1):13-21.

Maternal smoking during pregnancy elevates risk for later child behavior problems. Because prior studies considered only Western settings, where smoking cooccurs with social disadvantage, we examined this association in Yugoslavia, a different cultural setting. Mothers enrolled in pregnancy as the low-exposure group in a prospective study of lead exposure were interviewed about health, including smoking history. A total of 199 children were assessed on the Child Behavior Checklist (CBCL) at ages 4, 4 1/2, and 5 years. Average cumulative blood lead (BPb) was determined from serial samples taken biannually since delivery. Longitudinal analyses were derived from 191 children with available data on behavior and covariates. Smoking was unrelated to social adversity. Controlling for age, gender, birthweight, ethnicity, maternal education, and Home Observation for Measurement of the Environment (HOME) Acceptance, smoking was associated with worse scores on almost all subscales; BPb concentration was related to small increases in the Delinquency subscale. Daughters of smokers received significantly higher scores on Somatic Complaints compared to daughters of nonsmokers, consistent with other work relating biological factors and internalizing problems in young girls. Because the present smoking/child behavior associations persist after control for individual and social factors also related to behavior problems, possible biological mediators are considered.

Weber RFA, Pierik FH, Dohle GR, Burdorf A. **Environmental influences on male reproduction.** BJU International 2002;89(2):143-48.

Considerable concern has been raised in recent publications that oestrogen-like compounds in either food or the environment cause adverse effects on reproductive health. There is clear evidence that reproductive disruption in wildlife may be caused by environmental pollutants and more specifically by endocrine-disrupting compounds. The increase in the incidence of disorders of the male reproductive tract (e.g. testicular cancer, cryptorchidism, hypospadias) and the possible decline of sperm quality led to the hypothesis in 1993 that the reported increases stem from fetal or neonatal exposure of the developing male to oestrogens. Cryptorchidism, hypospadias, testicular cancer and poor semen quality have also been proposed to be symptoms of one underlying cause, the testicular dysgenesis syndrome, which may develop during fetal life under the influence of environmental factors. However, there is only circumstantial evidence in humans that exposure to endocrine disruptors, especially diethylstilbestrol, during pregnancy causes problems of reproductive health. Oestrogen-like effects have been reported for a variety of naturally occurring oestrogens (so-called phytoestrogens) and for numerous synthetic compounds. The critical issue is whether there are sufficiently high levels of endocrine disruptors in the ambient environment to exert adverse health effects on the general population.

Weiss B. **Vulnerability of children and the developing brain to neurotoxic hazards**. Environmental Health Perspectives 2000;108:375-81.

For much of the history of toxicology, the sensitivity of the developing organism to chemical perturbation attracted limited attention. Several tragic episodes and new insights finally taught us that the course of early brain development incurs unique risks. Although the process is exquisitely controlled, its lability renders it highly susceptible to damage from environmental

chemicals. Such disturbances, as recognized by current testing protocols and legislation such as the Food Quality Protection Act, can result in outcomes ranging from death to malformations to functional impairment. The latter are the most difficult to determine. First, they require a variety of measures to assay their extent. Second, adult responses may prove an inadequate guide to the response of the developing brain, which is part of the reason for proposing additional safety factors for children. Third, neuropsychological tests are deployed in complex circumstances in which many factors, including economic status, combine to produce a particular effect such as lowered intelligence quotient score. Fourth, the magnitude of the effect, for most environmental exposure levels, may be relatively small but extremely significant for public health. Fifth, changes in brain function occur throughout life, and some consequences of early damage may not even emerge until advanced age. Such factors need to be addressed in estimating the influence of a particular agent or group of agents on brain development and its functional expression. It is especially important to consider ways of dealing with multiple risks and their combinations in addition to the prevailing practice of estimating risks in isolation.

Whitaker RC, Dietz WH. **Role of the prenatal environment in the development of obesity**. Journal of Pediatrics 1998 May;132 (5):768-76.

Establishing that prenatal life is a critical or sensitive period for the development of obesity may focus basic research and clinical prevention efforts on this period. This review summarizes evidence that the intrauterine environment influences the risk of later obesity and considers the mechanisms by which this may occur. The association between birth weight and adult weight suggests that there are enduring effects of the intrauterine environment on later obesity risk. We examine whether the maternal factors of diabetes, obesity, and pregnancy weight gain alter the intrauterine environment and thereby increase the risk of later obesity in the offspring. Of these maternal factors, evidence is strongest for the role of maternal diabetes. No single mechanism explains how these maternal factors could change the intrauterine environment to increase obesity risk. However, all potential mechanisms involve an altered transfer of metabolic substrates between mother and fetus, which may influence the developing structure or function of the organs involved in energy metabolism.

Zender R, Bachand AM, Reif JS. **Exposure to tap water during pregnancy**. Journal of Exposure Analysis and Environmental Epidemiology 2001;11(3):224-30.

Studies of disinfection byproducts (DBPs) in drinking water and risk of adverse reproductive outcome have usually relied on approximate measures of exposure. Individual differences in consumption of bottled or filtered water, variability in tap water consumption at home and at work, dermal and inhalation exposure to volatile contaminants, and changes in residency during pregnancy may lead to exposure misclassification. We characterized exposures to tap water and other risk factors among 71 pregnant and 43 non-pregnant women attending public health clinics. Nearly all residences had a municipal water source, but 25% of women drank filtered or bottled water. Fifty percent of the women in our sample reported working outside the home where, on average, one third of their daily water intake took place. Pregnant women consumed more water than non-pregnant women (3.4 vs. 3.0 total l/day), especially cold tap water at home (1.8 vs. 1.3 l/day, 95% CI for the difference=0.1, 0.9). Patterns of showering were similar for both groups of women, but pregnant women were more likely to bathe and to bathe more frequently. The prevalence of smoking was lower among pregnant women (22.5% vs. 32.6%), as was the consumption of alcohol (4.2% vs. 53.5%, 95% CI for the difference=-64.9, -33.7). Thirty-two

percent of women had moved during their current pregnancy. The data reaffirm the importance of collecting individual-level data for water consumption and exposure to potential confounders to avoid misclassification bias. This study is the first to target women of low socio-economic status (SES) and therefore of particular interest in studies of adverse reproductive outcomes for which this group is at increased risk.